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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,087	09/29/2003	Jianzhu Chen	0492611-0507 (MIT 10396)	2178

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EXAMINER	
CHONG, KIMBERLY	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
11/09/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/674,087	CHEN ET AL.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *111-113* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *111-113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 08/23/2010 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 02/22/2010 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 101-110 have been canceled and new claims 111-113 are currently under examination. **No claims are allowable.**

New Claim Rejections – Necessitated by Claim Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 111-113 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 111-113 drawn to methods of inhibiting a transcript associated with a influenza virus, or methods of treating an influenza virus nucleoprotein or a clinical condition associated with overexpression or inappropriate expression of an influenza transcript, comprising administering an siRNA, shRNA, and a microRNA in combination with a cationic peptide.

Applicant submits support for microRNAs can be found in paragraph 66. Paragraph 66 is copied below and does not adequately provide support for microRNAs in the claimed invention:

0066] These small dsRNAs (siRNAs) act to silence expression of any gene that includes a region complementary to one of the dsRNA strands, presumably because a helicase activity unwinds the 19 bp duplex in the siRNA, allowing an alternative duplex to form between one strand of the siRNA and the target transcript. This new duplex then guides an endonuclease complex, RISC, to the target RNA, which it cleaves ("slices") at a single location, producing unprotected RNA ends that are promptly degraded by cellular machinery (FIG. 2). **As mentioned below, additional mechanisms of silencing mediated by short RNA species (microRNAs) are also known** (see, e.g., Ruvkun, G., Science, 294, 797-799, 2001; Zeng, Y., et al., Molecular Cell, 9, 1-20, 2002). It is noted that the discussion of mechanisms and the figures depicting them are not intended to suggest any limitations on the mechanism of action of the present invention. [emphasis added].

The recitation of microRNAs in the specification is in a paragraph related to background information of dsRNAs. A search of the entire specification as filed does not reveal microRNAs in any other context except as above. MicroRNAs was not contemplated as being used in the claimed method of inhibiting a target transcript.

If Applicant believes that such support is present in the specification and claimed priority documents, Applicant should point, with particularity, to where such support is to be found.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 111-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abe et al. (European Journal of Pharm. Sci, 2001 of record IDS filed 09/12/2005), Tuschl et al. (WO 02/44321 of record), Astriab-Fisher et al. teach (Biochemical Pharmacology, 2000. Vol. 60, pp.83-90 of record), Herweijer et al. (US 2002/0165183) and evidenced by Caplen (Expert Opin. Biol. Ther. 2003, 3(4): 575-586 of record) and Trubetskoy et al. (US 2004/0162235 of record).

The claims are drawn to methods of inhibiting a transcript associated with a influenza virus, or methods of treating an influenza virus nucleoprotein or a clinical condition associated with overexpression or inappropriate expression of an influenza

transcript, comprising administering an siRNA in combination with a cationic peptide, and wherein said administration is vascular.

Abe et al. teach targeting an antisense compound to a gene encoding the influenza viral nucleoprotein (NP). Abe et al. teach sequence specific inhibition of expression in vitro using said antisense compounds delivered using liposomes (see Table 2). Abe et al. teach intravenous delivery of antisense compounds to mouse infected with influenza virus and teach a reduction in the viral target mRNA and a decrease in virus titer in the lungs (see pages 65-68). Abe et al. do not teach using a siRNA targeted to a viral nucleoprotein or teach using a siRNA and a cationic peptide.

Tuschl et al. teach the use of siRNA compounds to inhibit gene expression. Tuschl et al. teach siRNA are the new alternative to antisense compounds and have improved efficacy and safety (see page 3). Tuschl et al. teach a method of using siRNA to infect cells of mammals and teach modulating of the function of a target gene in numerous tissues and cells, such as a viral target gene (see page 8). Tuschl et al. teach the siRNA can be delivered using a carrier system (see page 8) and teach the siRNA can be administered by injection. Additionally, Tuschl et al. teach a vector capable of expression of a siRNA (see page 7).

Astriab-Fisher et al. teach inhibition of gene expression using oligonucleotides conjugated to cationic peptides. Astriab-Fisher et al. teach one of the major problems with the use of oligonucleotides is delivery to the cytoplasm and nucleus of the cells and teach it was known in the art to try and overcome this problem by complexing the oligonucleotide with liposomes but one major liability with this approach is that

liposomes do not work well in the presence of serum and therefore are not effective in vivo situations (see page 83). Astraib-Fisher et al. teach the use of delivery cationic peptides such as Tat protein and Antennapeida protein which are capable of intracellular delivery of molecules across cell membranes (see page 83-85).

Herweijer et al. teach methods of delivery of nucleic acid molecules into cells wherein the nucleic acid can be siRNA and the delivery agent can consist of a cationic peptide such as a polylysine or polyarginine (see at least paragraphs 0153-0157).

It would have been obvious to one of skill in the art to substitute a siRNA molecule for the antisense molecule in the method of inhibiting an influenza viral gene taught by Abe et al. It would have further been obvious to use the cationic peptide to efficiently deliver the siRNA to the cell of interest.

It was well known at the time of the instant invention that silencing of gene expression using siRNA was more efficient and sequence specific as compared to antisense or ribozyme technologies. One of ordinary skill in the art would have clearly substituted the antisense compound taught by Abe et al. with a siRNA in a method of inhibiting an influenza viral gene expression in infected organs of a subject. Therefore, because as demonstrated by Tuschl et al., siRNAs were known to be more efficient at silencing gene expression, one of ordinary skill in the art at the time the invention was made would have clearly substituted the antisense molecule for a siRNA to target the influenza viral NP gene.

It was further well known that one of the major problems with the use of oligonucleotides is delivery to the cytoplasm and nucleus of the cells and that siRNA

has the same delivery issues as antisense oligonucleotides as evidenced by Caplen (Expert Opin. Biol. Ther. 2003, 3(4): 575-586) who states "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system, have been problems the gene therapy field has struggled with for over a decade now" (see page 581, last paragraph). It was also well known in the art that using peptide-nucleic acid complexes could overcome these problems and therefore one of ordinary skill in the art would have used a delivery agent as taught by Astriab-Fisher et al. Herweijer et al. demonstrates that it was it was routine to use a delivery agent such as a cationic peptide to deliver nucleic acids into cells and teach this could be used with any nucleic acid such as siRNA. Thus the skilled artisan would have been motivated to make a siRNA-peptide conjugate to target a transcript associated with influenza virus.

There would have been a reasonable expectation of success at using a cationic peptide for delivery of a siRNA into cells, given Astriab-Fisher et al. teach delivery of a nucleic acid using a cationic peptide and as taught by Herweijer and evidenced by Trubetskoy et al., who teach routine methods of using compositions comprising siRNA and cationic agents to deliver said siRNA into cells in vivo (see Example 7).

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant argues that one of ordinary skill in the art would not necessarily have been motivated to utilize the same delivery methods for antisense technology and RNAi technology because each have very different chemical properties and behaviors from one another. This argument is not convincing because both antisense and RNAi molecules are nucleic acid molecules with the same issues regarding delivery and as stated previously and reiterated herein, it was well known that one of the major problems with the use of oligonucleotides is delivery to the cytoplasm and nucleus of the cells and that siRNA has the same delivery issues as antisense oligonucleotides as evidenced by Caplen (Expert Opin. Biol. Ther. 2003, 3(4): 575-586) who states "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system, have been problems the gene therapy field has struggled with for over a decade now" (see page 581, last paragraph). It was also well known in the art that using peptide-nucleic acid complexes could overcome these problems and therefore one of ordinary skill in the would have use a delivery agent as taught by Astriab-Fisher et al. to complex with siRNA in the method of inhibiting the influenza NP viral gene.

Applicant argues that it was known in the art that the use of cationic polymers were effective because they bound to and condensed large DNA molecules and the fact that RNAi uses short RNA molecules suggests "that they probably cannot be

condensed much further" and "those of ordinary skill in the art at the time when the invention was filed might have expected that these different kinds of molecules having different chemical and structural properties would behave differently if delivery of these molecules were attempted". Applicant provides no evidence that one of ordinary skill in the art would not use cationic polymers with siRNA because the molecules cannot be condensed further. Applicant further provides no evidence that one of ordinary skill in the art would have expected that these different molecules would behave differently if delivery were attempted using cationic polymers particularly given antisense molecules are short nucleic acid molecules. The prior art above demonstrates that antisense oligonucleotides 20 nucleotides in length can be conjugated with peptides and delivered to cells (Astriab-Fisher) and because Herweijer et al. teach a delivery agent such as claimed can be complexed with siRNA, one of ordinary skill in the art would have expected to be able to use the claimed delivery agent with a siRNA.

Thus the invention would have been obvious at the time of filing as stated above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 111-113 are provisionally rejected under the judicially created doctrine of double patenting over claims 12, 22 and 24-27 of copending Application No. 11/259,434. This is a provisional double patenting rejection since the conflicting claims have not yet been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of the patent are drawn to patently indistinguishable subject matter.

The claims are drawn to methods of inhibiting a transcript associated with a influenza virus, or methods of treating or preventing or treating an influenza virus or a clinical condition associated with overexpression or inappropriate expression of an influenza transcript, comprising administering an siRNA in combination with a cationic polymer, wherein said administration may be intravenous or intranasal, or is inhaled, or is delivered by aerosol, or wherein said inhibition is in the lung, or not in the lung, or wherein said combination is delivered with a delivery enhancing agent which may be an antibody or fragment or ligand.

Claims 12, 22 and 24-27 of co-pending Application No. 11/259,434 are drawn to a method of treating influenza virus infection comprising contacting the host cells with an antiviral compound comprising an antisense oligonucleotide wherein the

oligonucleotide is conjugated to a polypeptide that enhances uptake of the compound into the host cell. Co-pending Application No. 11/259,434 does not teach inhibiting expression of influenza virus or treating influenza virus using a siRNA and do not teach using a delivery agent such as a cationic polymer. Tuschl et al. (WO 02/44321) teach the use of siRNA compounds to inhibit gene expression. Tuschl et al. teach siRNA are the new alternative to antisense compounds and have improved efficacy and safety (see page 3). Gautam et al. (Molecular Therapy 2000, Vol. 2(1); 63-70) teach a method of efficiently delivery nucleic acids along with a cationic polymer, polyethyleneimine, into the lungs of a mouse (see Figure 1). It would have been obvious and one of skill in the art would have been motivated to use an siRNA in a method of treating influenza virus given Tuschl et al. teach siRNAs are the new alternative to antisense therapeutics.

Thus claims 12, 22 and 24-27 of co-pending Application No. 11/259,434 anticipates claims 111-113 of the instant application. This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 103

The rejection of claims 101-110 under 35 U.S.C. 103(a) as being unpatentable over Abe et al. (European Journal of Pharm. Sci, 2001 of record IDS filed 09/12/2005), Tuschl et al. (WO 02/44321 of record), Astriab-Fisher et al. teach (Biochemical Pharmacology, 2000. Vol. 60, pp.83-90 of record), Lewis et al. (US 2003/0125281 of record) and evidenced by Caplen (Expert Opin. Biol. Ther. 2003, 3(4): 575-586 of

record) and Trubetskoy et al. (US 2004/0162235 of record) is withdrawn as the claims have been canceled.

Double Patenting

The rejection of claims 101-110 under the judicially created doctrine of double patenting over claims 12, 22 and 24-27 of copending Application No. 11/259,434 is withdrawn as the claims have been canceled.

No claims are allowable.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact Acting SPE Heather Calamita at 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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